

Ingredient Review:

Calcium and Over-the-counter Products

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Q. *I know calcium is important for bone health, but recently I've seen it in skin care products. What can calcium possibly do for the skin?*

A. Calcium is one of the most important minerals on the planet. Gaining its name from *calx*, the Roman word for “lime”—calcium oxide, calcium is the fifth most abundant element in the earth's crust and is an essential component of leaves, teeth, shells and bone.

While it's true that calcium is used to build bone, if the mineral is not readily available from one's diet, the body also will tear down bone to free-up calcium needed in other areas. If bone is ransacked for calcium over a period of years, bones throughout the body become weak and break easily. Such is the case with the bone disease osteoporosis—*osteo*: bone; *porosis*: porous—that derives its name from the holes which can be seen in weakened bones where calcium stores have been depleted. An estimated 25 million women and five million men have osteoporosis, with one-third to one-half of all post-menopausal women being affected, and smokers showing higher risk than non-smokers.

Calcium is of more importance than just for bone-building and maintaining bone strength. This mineral figures in many biological processes throughout the body, most important of which are energy production; heartbeat regulation; hormone storage and release; regulation of enzymatic reactions; muscle contractions; blood clotting; the formation of cell membranes and utilization of vitamin B-12—a crucial vitamin for deoxyribonucleic acid (DNA) synthesis; and to calm nerves during stress. In the skin, calcium plays a role in the production and maturation of epidermal cells and the creation of the skin's barrier—including a variety of lipids that maintain the barrier's ability to hold out irritants and keep skin moist, supple and youthful. It's interesting that dry skin, skin sensitivity and osteoporosis all increase significantly after menopause. Therefore, during analysis, if a client indicates osteoporosis as a medical condition, you may want to ask if dry skin, irritation or skin sensitivity also are problems.

Calcium in the diet

Increasing calcium in the diet has definite benefits to prevent bone loss and may have an effect on other biological processes where calcium is required. The daily U.S. Adequate Intake (AI) recommendations published in 1997 set dietary calcium for adults under 50 who aren't pregnant or lactating at 1,000 milligrams, and 1,200 milligrams for adults over 50. Studies show that the average intake for Americans under 50 is around 720 milligrams while those over 50 often take in even less of the mineral. Calcium supplements often are recommended by physicians, or your client may choose to select calcium-rich foods such as milk and milk products, eggs, broccoli, turnip greens, kelp, almonds, sardines, salmon, calcium-enriched foods including orange juice and breakfast cereals, and caviar.

While supplementation and diet can help supply the rest of the body with calcium, the skin may not get its fair share since this organ isn't needed for immediate survival. In an effort to increase calcium in the skin, some skin care companies now are including calcium in leave-on products such as moisturizers, night treatments and serums. The problem is that calcium is highly reactive with

air and water, so it must be bound to other elements for stability. Recently, researchers in France found that linking calcium to l-pyrrolidone carboxylic acid (PCA)—a hydrating molecule that contributes 12% of the skin's natural moisturizing factors—increased calcium delivery into the skin. In this capacity, PCA is known as a pilot molecule, guiding calcium through the skin's stratum corneum barrier into the heart of epidermal keratinocytes waiting below it. The calcium then can help these cells reproduce, mature and create a stronger, more hydrated and resilient barrier while also having a collagen-protective action in the dermis.

Unlike other ingredients that influence lipid production by keratinocytes in an effort to repair skin barriers that have been damaged from sun, chemical exposure, stress or aging, calcium-PCA has been shown to significantly increase all of the major lipids in the stratum corneum, including ceramides 1 and 2, phospholipids, glycerylceramides, diglycerides, triglycerides, cholesterol and cholesteryl sulphate—resulting in more complete repair. Calcium also strengthens the cell membranes and linkages between keratinocytes, helping them create a stronger barrier against irritants and moisture loss as they die and become corneocytes when they enter the stratum corneum. It is this structure of dead corneocyte cells glued together with moisture-holding lipids that create the skin's barrier.

Anti-aging effect

Calcium-PCA also has an anti-aging effect on the dermis. When skin is stressed or attacked by aggressive agents, a messenger known as interleukin-1alpha (IL-1a) is released. Under the direction of IL-1a, epidermal keratinocytes release destructive enzymes called matrix metalloproteinases (MMPs). MMP-1, also known as collagenase, destroys skin-plumping collagen fibers in the dermis. For this reason, inflammation due to stress, sun, chemical exposure and some diseases contributes to skin aging when MMP-1 and other members of this destructive enzyme group rip through the dermis, leading to a collapse of tissue that results in wrinkles and loss of firmness. Calcium-PCA is reported to reduce the presence of MMP-1 by 35% in keratinocyte cell cultures.

Q. *What does OTC mean? I hear it a lot, but I don't feel comfortable asking anyone I know, since everyone else seems to know what it means.*

A. OTC means over-the-counter. When a medical practitioner says it, the term can refer to cosmetic products sold in a retail environment, such as salons, drug and department stores, but OTC has a legal definition, too. It refers to drugs that are sold over-the-counter without a prescription.

Drugs, regardless of whether they're sold via a prescription or without, are defined in the Food, Drug and Cosmetic Act passed by Congress in 1938 as "(A) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease . . . and (B) articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201 (1)]. There's also such a thing as a "cosmetic-OTC drug" that performs a cosmetic action such as beautifying, cleansing or moisturizing in combination with having a drug effect. Examples of these are moisturizers or lipsticks intended to offer ultraviolet (UV) protection or antibacterial facial cleansers.

You'll notice that the definitive word here is "intended." It is the intent of the drug seller that makes a product a drug, not the

fact that it may be affecting the structure or function of the body or offers therapeutic value. A cosmetic product, such as a moisturizer, may stimulate lipid production in epidermal cells or protect collagen from being destroyed by inflammation processes, but as long as the seller of the product does not make these statements in connection to the product, the moisturizer does not meet the definition of a drug.

Intent usually is determined from label claims made for the product. These can be written statements printed directly on the product's label, in promotional literature, displays, advertising and on the Internet, as well as what are voiced by the seller to a consumer. Extended label claims can occur when information published by someone other than the product's maker is offered to the consumer to review, then the information is linked directly to the product. If claims are made in the article for the product or an ingredient in the product, the claims would extend to the product itself. An example of this is when a magazine article offers information about the collagen-stimulating properties of an ingredient—a claim affecting skin's structure—and a retailer hands out or displays the article in connection to a product that features the ingredient. The skin structure claim made in the article most likely would extend to the product offered by the retailer, resulting in a drug claim for the product. The U.S. Food and Drug Administration (FDA), the government organization charged by Congress to regulate the FD&C Act, also has stated that intended claims can be judged by consumer expectations of the product's effects or the inclusion of ingredients that are known to the public and industry to have a therapeutic use, such as fluoride's ability to prevent tooth decay.

Beauty industry links

There are more than 80 therapeutic categories for OTC drugs, with more than 20 of them linked to the beauty industry. These include acne preparations; sunscreens; skin bleach; skin protectants; anti-dandruff, seborrheic dermatitis and psoriasis treatments; hair growth and hair loss prevention; antiperspirants; and topical anti-inflammatories, antimicrobials and anti-fungals.

Products featuring claims such as "restores hair growth," "reduces cellulite," "treats varicose veins" and "revitalizes cells"—where the intended use of the product is to treat or prevent disease or otherwise affect the structure or function of the body—are viewed as drugs, according to the FDA's Web site. The same is true for aromatherapy oils that feature claims such as "aids with sleep" or "quenches the desire to smoke." According to the same Web site, these also meet the definition of a drug. These types of claims can land the product in the realm of "new drug" if they are not covered by a recognized OTC category. If a product is identified as being a new drug, the manufacturer must go through an approval process that's very different and much more expensive and more time consuming than products that fall under recognized OTC categories.

Another area that could put a product's legal status in question involves products that are intended to affect the skin under the stratum corneum. FDA insiders have stated they view the area under the skin's barrier, known as the viable epidermis, as the living area of skin. Therefore, products claiming to affect the structure or function of the skin below the stratum corneum could be considered drugs.

Frequently, anti-aging products make claims that dip below the stratum corneum, or they simply make the promise of anti-

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aging. Unless anti-aging is defined clearly in other product claims as having only a cosmetic effect, it could be considered a drug claim. Since there is no OTC category for anti-aging, these products may be considered new drugs that must go through the process of petitioning FDA for new drug status.

Cosmeceuticals

A new product category on the beauty scene is “cosmeceuticals.” Products sold under the guise of cosmeceuticals often are cosmetic products—usually skin creams and serums—with drug-like actions stated by the manufacturer to elevate the product above others in its class. Since there is no legal definition for cosmeceutical—it is a marketing term, not one of law—when this name is attached to a cosmetic product that features claims about effecting the structure or function of the skin, or makes other therapeutic promises, these products could be deemed drugs, not cosmetics.

Why is all this important? Unlike a cosmetic, which, if it has been proven safe for use by its maker and is legally labeled or features a warning statement that the product has not been proven safe for use—can be sold without pre-market approval, drugs are subject to FDA approval before entering the marketplace. They also must be manufactured under Good Manufacturing Practices (GMPs) set forth by the FDA and produced in a drug-registered facility, whereas cosmetic manufacturers have no specific GMP regulations for the making of their products.

If a product conforms to a series of requirements that are outlined in an FDA document known as a monograph, the maker can introduce it into the marketplace without further FDA approval. Monographs describe the type of drug, for example, a sunscreen; the drug’s function; the active ingredients and the percentages recognized as safe and effective for this condition, known as Category I ingredients; ingredients not recognized as safe or effective, Category II ingredients; ingredients for which there is inadequate data to make a determination whether an ingredient is safe or effective—for proposed monographs only that have not been finalized by the FDA; formulation requirements that must be followed when producing the drug; any testing procedures that must be conducted to prove the drug is working; and label requirements, including warnings and marketing claims that can be made for the drug.

Active ingredients

Many OTC drugs also must feature what’s called the “Drug Facts” label, a new labeling format required by the FDA to clearly define the OTC drug ingredients identified as “Active Ingredients,” their purpose, intended use of the drug, warnings, clear directions, and a “Questions?” or “Questions or Comments?” section that provides the telephone number or a source to answer questions about the product. If the product also is delivering cosmetic benefits, such as a moisturizer or lipstick with sunscreen, an anti-dandruff shampoo, or an antiperspirant deodorant, the cosmetic ingredient list also must be included under the heading “Inactive Ingredients.” This latter part has some manufacturers up in arms because the word “inactive” implies the cosmetic ingredients in the formula aren’t doing anything. That perception makes it rather difficult to get a client to accept that the glycerin or lipids or minerals in the product actually are yielding any benefit.

Sometimes OTC claims are made for ingredients that are present in an OTC product but are not listed under the “Active Ingredient” heading. Examples of this are carrot or walnut oil, makeup pigments other than titanium dioxide that feature sunscreen or sun protection claims, or licorice or vitamin C with skin lightening claims. Even though these ingredients are in the OTC product, and even if the manufacturer has clear evidence these ingredients are delivering part of the OTC effect, only those ingredients listed under the “Active Ingredient” heading can be linked to the OTC claim. On the other hand, if an OTC ingredient is listed in the “Inactive Ingredient” section, it is probably not being used to achieve the OTC result. For instance, if you see a sunscreen such as titanium dioxide listed under the cosmetic ingredient label, it either isn’t be-

ing used at the required percentage to deliver sun protection, or the product isn't an OTC sunscreen and hasn't been produced under the required manufacturing processes, in a drug-registered facility, or cleared the performance test required in the OTC sunscreen monograph.

There is one caveat to all this: monographs are expected to be finalized by the FDA after having been reviewed and commented upon by the public and industry. The OTC Drug Review process began on May 11, 1972, and, for some monographs, including sunscreens and skin bleaches, the process has yet to be finalized. While it generally is understood that the last published version of the monograph offered for review by the public and industry is the version that must be followed by makers and sellers of these products, even if the monograph hasn't been finalized, products that were on the market before the 1972 start date may be marketed without specific approval pending publication of the final monograph.

Know the difference

If you have a question regarding whether or not a product is an OTC drug, you can do several things:

- 1. Review the product's claims.** If it features claims regarding acne, sun or UV protection, anti-inflammation, skin lightening, has a stated SPF or features other statements that clearly put it in an OTC category, it probably is an OTC drug or a cosmetic-OTC drug product.
- 2. Look for ingredients under the heading "Active Ingredients."** These are usually at the top of the ingredient

list or product label. Remember that "Inactive Ingredients" or "Other Ingredients," a term still used by some manufacturers, describes the cosmetic ingredients that make up the product, while "Active Ingredients" identifies the ingredients allowed in the OTC monograph.

- 3. Ask your manufacturer if the product is an OTC drug.** A representative should be able to offer an answer quickly and provide any supporting data for the company's statement if you ask for it.
- 4. Ask your manufacturer for a copy of the monograph-required performance test.** If you have determined the product is an OTC drug, but you are having problems with it, for instance, clients frequently complain of sunburn after 30 minutes of wearing an SPF 15 sunscreen, you can ask for a copy of the monograph-required test results conducted on the product. If the manufacturer won't or can't produce the results, it may be an indication that the product does not meet the OTC requirements.

If you'd like to learn more about OTC drugs and cosmetics, visit the FDA's Web site at www.fda.gov and click on the appropriate icons. You also can go directly to the Center for Drug Evaluation and Research, the division of FDA that oversees OTC drugs, at www.fda.gov/cder/offices/otc for information about OTCs. For information about specific OTC monographs, enter the monograph name, for instance, Sunscreen Monograph, in the space marked "Search" on the CDER homepage or go to http://www.fda.gov/cder/otcmonographs/rulemaking_index.htm. ■